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(21) International Application Number: PCT/EP98/04238 (22) International Filing Date: 8 July 1998 (08.07.98) (30) Priority Data: MI97A01628 9 July 1997 (09.07.97) IT (71) Applicants (for all designated States except US): GEANGE LIMITED [IE/IE]; 17 Earlsfort Terrace, Dublin 2 (IE). EURODRUG LTD. [CN/CN]; Java Comm. Centre, Room 1501, 124-134 Java Road, North Point, Hong Kong (CN). LIPOTEC S.A. [ES/ES]; Calle Santa Eulalia 240, E-08902 L'Hospitalet de Llobregat (ES). (72) Inventors; and (75) Inventors/Applicants (for US only): VAN GULIK, Fred [NL/CN]; Eurodrug Ltd., Java Comm. Centre, Room 1501, 124-134 Java Road, North Point - Hong Kong (CN). PARENTE, Antonio [ES/ES]; Lipotec s.a., Calle Santa Eulalia 240, E-08902 L'Hospitalet de Llobregat (ES). (74) Agents: TRUPIANO, Federica et al.; Brevetti Europa S.r.l., Piazza Bernini, 6, I-20133 Milano (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DIPHOSPHONIC ACID SALTS FOR THE TREATMENT OF OSTEOPOROSIS (57) Abstract Disphosphonates, or their salts between disphosphonic acids and linear, branched substituted and non-substituted, cyclic, hetero-cyclic and aromatic amino-alcohols, and their use in the treatment of osteoporosis, and pharmaceutical compositions that contain at least one diphosphonate as active principle for the treatment of osteoporosis.		

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DISPHOSPHONIC ACID SALTS FOR THE TREATMENT OF OSTEOPOROSIS

OBJECT OF THE PRESENT INVENTION

5

Object of the present invention are salts of diphosphonic acids or diphosphonates and a procedure for their preparation.

Object of the present invention is also the use of mentioned salts of diphosphonic acids or diphosphonates for treatment of osteoporosis.

10

Object of the present invention are again pharmaceutical compositions which contain, as active principle, the mentioned salts of diphosphonic acids or diphosphonates and the use of these compositions in the treatment of osteoporosis.

15

STATUS OF THE TECHNIQUE

As well known osteoporosis is a disease of the skeleton that is characterised by the disarrangement and by the loss of bone tissue, with increase of skeleton fragility and predisposition to fractures.

As an example, is reported that in US this disease
20 afflicts more than 25 millions of persons and it causes 1.300.000 fractures every year.

The social cost is consequently very high accounting for more than 10 billions of US dollars per year. The same figures are reported in Europe and in Japan.

25

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The elderly is the population with the highest risk. Unfortunately the problem is becoming progressively more serious in the view of the progressive grow old of population. A forecast of the fracture incidence in the
5 future sixty years assumes an increase of at least three times. Women are more exposed than men, particularly during the first 5 years after the menopausal period.

At present, from a therapeutic viewpoint, either a mono-therapy with fluorides, as reported by Melmon & Morrelli,
10 Clinical Pharmacology: Basic Principles in Therapeutics, 497 (1992), N. Engl. J. Med. 306,446 (1982) is used, or addition use of combined therapies with calcium, fluoride and oestrogens are reported to retain some advantages as compared to the mono-therapy.

15 Alternatively, another class of compounds prescribed for the treatment of osteoporosis includes disphosphonates; these agents are mostly administered by oral route, but besides having the unsolved inconvenient of a poor absorption (from 1 to 5% of dose), they also develop, as
20 primary adverse events, oesophagitis and gastrointestinal disorders of moderate-severe intensity.

To overcome this inconvenient, several clinical studies have been carried out, in the search of new compounds
25 that combine a high pharmacological activity together

with a better tolerability and increased bioavailability as compared to known available compounds.

For example, in the treatment of urolithiasis and for inhibition of bone resorption, diphosphonic acids and their salts are described in the US patent 4,621,077; namely, the biological activities of mentioned phosphonic acids or their corresponding sodium salts are reported. The degree of absorption, i.e. the bioavailability, of those compounds resulted however very low and for this reason, in order to achieve in the body active concentrations of the active principle, high doses had to be administered with consequent occurrence of gastrointestinal adverse reactions which worsen tolerability.

OBJECTIVES OF THE INVENTION

Objective of the present invention is to make available diphosphonates that have an increased bioavailability when administered by oral route.

Objective of the present invention is also to make available diphosphonates that are more effective in the treatment of osteoporosis while retaining a lower incidence of oesophagus and gastro-intestinal adverse events as compared to those known compounds already available.

Again, objective of the present invention is to make available diphosphonates which can be administered both by oral or intravenous route.

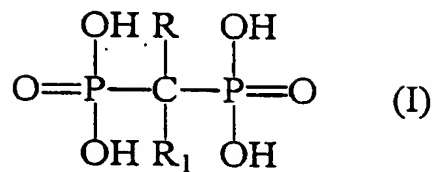
5 Again, objective of the present invention is to make available diphosphonates that display an improved therapeutic index in treatment of osteoporosis as compared to the known drugs at present used in the medical practice.

10 Objective of the present invention is also to make available a procedure for the preparation of diphosphonates.

15 Objective of the present invention is also to make available pharmaceutical formulations, containing at least one diphosphonate as active principle, easy to be administered, well tolerated and able to allow a high therapeutic index.

DESCRIPTION OF THE INVENTION

20 These and other objectives with further advantages which are clarified in the description below, are obtained by diphosphonates or salts of diphosphonic acids and linear, branched, substituted and non-substituted, cyclic, hetero-cyclic, aromatic amino-alcohol derivatives, said diphosphonates having the following general formula:



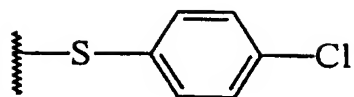
where $R=R_1$ or $R \neq R_1$ and R and R_1 are chosen among H, OH, Cl, linear or branched, substituted or not substituted alkyl groups, linear or branched, substituted or not substituted alkylidenic chain, or they are chosen among:

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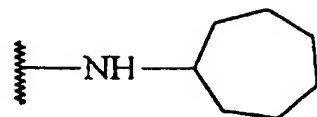
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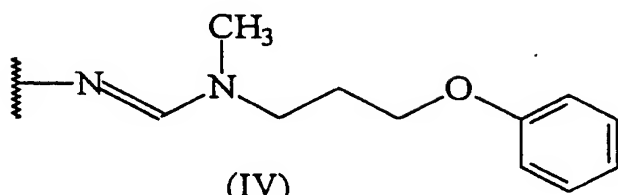
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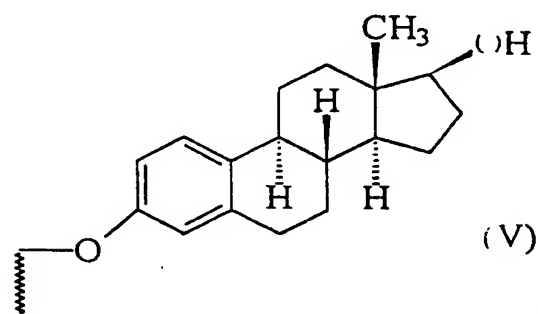
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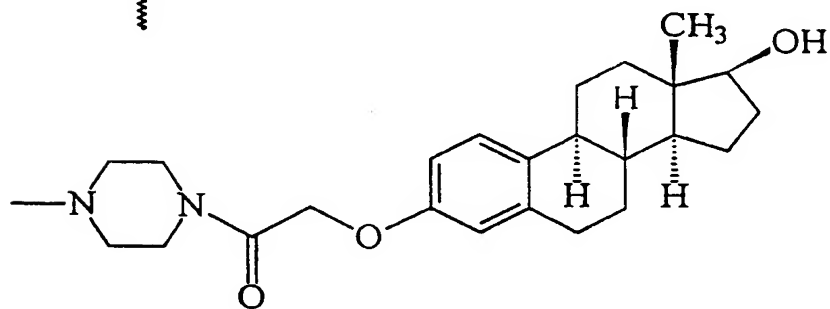
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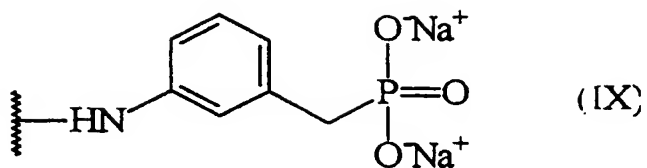
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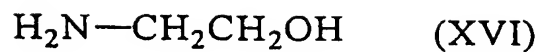
5 More particularly, according to the present invention, mentioned amino-alcohols are chosen among linear and branched amino-alcohols, and specifically they are chosen among:

10

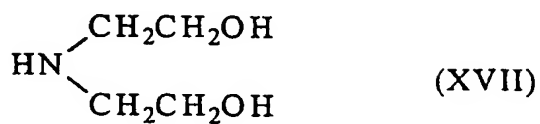
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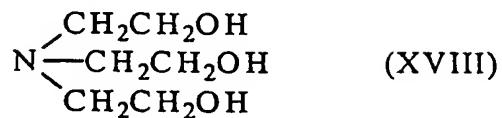
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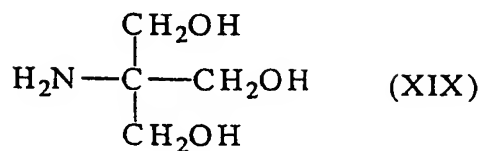
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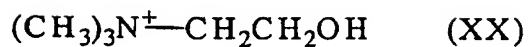
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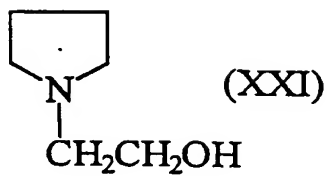


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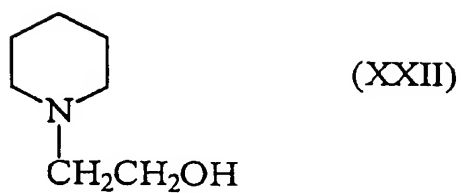


Always according to the present invention, mentioned amino-alcohols are cyclic and hetero cyclic amino-alcohols and are chosen among

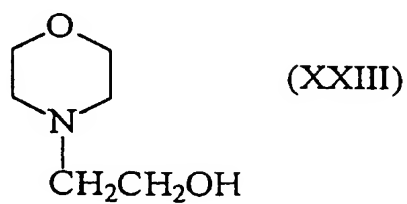
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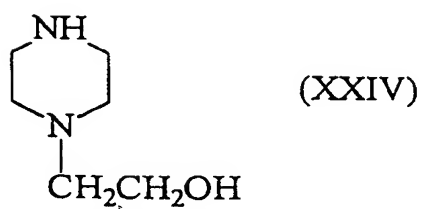
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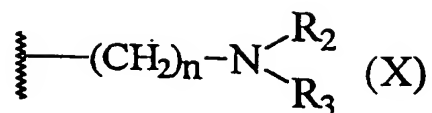


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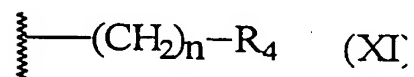
Again, according to the present invention, mentioned
substituted alkylidenic chain, defined in formula (I), is
chosen equal to:

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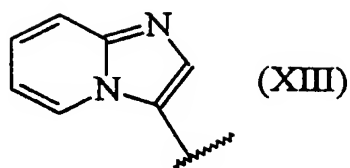
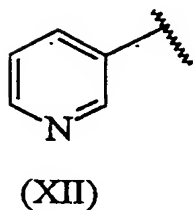
with n within 1 and 6, where $\text{R}_2 = \text{R}_3$ or $\text{R}_2 \neq \text{R}_3$ and R_2 and R_3 are chosen among H, linear or branched, cyclic, substituted or non-substituted alkyl groups, or R_2 and R_3 represent, together with the nitrogen atom N, an aliphatic or aromatic hetero-cycle.

Always according to the present invention, the substituted alkylidenic chain, defined in formula (I), is also chosen equal to

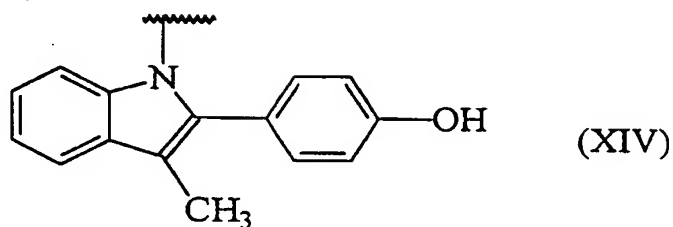


where n is within 1 and 6 and R_4 is chosen among:

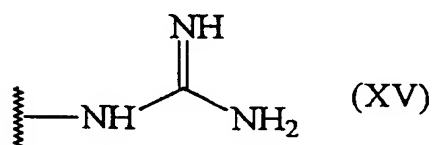
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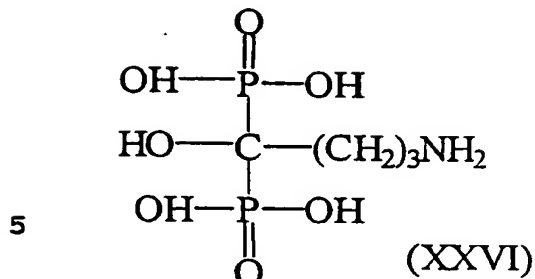


According to the present invention, of particular interest appeared the salt obtained between a diposphonic acid of general formula (I), where $R \neq R_1$, R is chosen equal to OH and R_1 is chosen as substituted linear alkyldenic chain of formula (X), where $n=3$, R_2 and R_3 are equal to H according to the following formula:

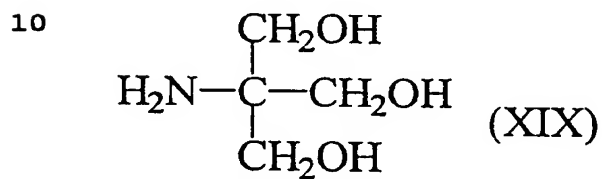
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25



or 4-amino-1-hydroxybutane-1,1-biphosphonic acid (alendronic acid) and one branched amino-alcohol of formula



or 2-amino-2-hydroxymethyl-1,3-propanediol (trometamine).

15 Mentioned salts, always according to the present invention, depending upon the preparation procedure, are formed by the residues corresponding to the diphosphonic acid and the amino-alcohol in a variable molar ratio, while they can be advantageously used in the treatment of osteoporosis. Mentioned molar ratios can vary between 1:1
20 and 1:2 (diphosphonic acid : amino-alcohol).

Diphosphonates according to the prior art, retain a non satisfactory pharmacokinetic profile, characterised by a very poor absorption from the gastro-intestinal tract,
25 with a systemic bioavailability ranging between 1 to 5 %

of the oral dose. About 50% of the absorbed dose is then eliminated with the urine in 24 hours, while the dose left is retained by bone tissue and afterwards eliminated very slowly.. The unabsorbed diphosphonate is instead
5 eliminated with the faeces.

This behaviour has to be attributed to the physico-chemical properties of the products, which being highly hydro-soluble hardly penetrate the lipid membranes. Oral doses much higher than those bioavailable are then
10 necessary to achieve and maintain a therapeutic effective concentration at the target site (bone), with consequent increase of the local gastro-intestinal adverse events like nausea and diarrhoea.

Diphosphonates according to the present invention, due to
15 the lower dissociation degree of the salt and to the physico-chemical properties of the amino-alcohol, are characterised by a lower water solubility and an increased lipid solubility as compared to the known diphosphonates (sodium salts).

20 These characteristics confer remarkable advantages in the absorption process trough the biological membranes, thus improving bioavailability.

In addition, diphosphonates of the present invention, did
25 show a promising pharmaco-toxicological profile in

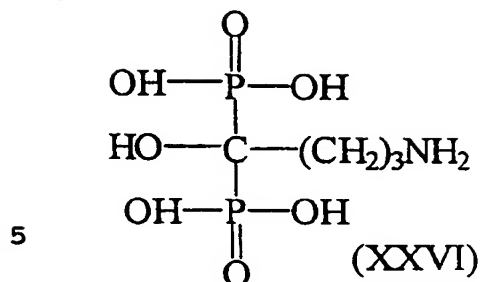
relation to the expected use in the therapy of osteoporosis.

The diphosphonates of the present invention show a good efficacy in stimulating bone growth, this being probably
5 due to the known property of amino-alcohols of subtracting toxic-radicals produced by reactive species.

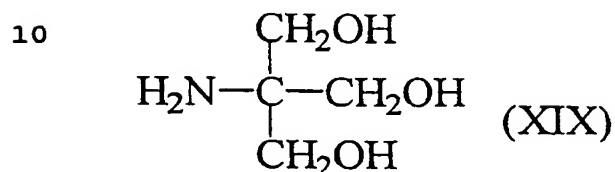
The diphosphonates of the present invention can be easily administered both by intravenous and oral route. In this
10 latter case, the use of pharmaceutical systems able to control the release of the active principle, are particularly advantageous. These systems include liposoms, niosomes and similar matrices, possibly added appropriate carriers which are of easy use and allow a
15 sustained release of the active principle.

The diphosphonates of the present invention are advantageously prepared by reacting a solution or
suspension of diphosphonic acid of general formula (I) with an amino-alcohol dissolved in a proper solvent; the
20 reaction product (salt) between the diphosphonic acid and the amino-alcohol, obtained by cooling the resulting solution, is then purified according to known techniques.

As a non-limitative example of the present invention, some examples referring to the preparation of the salt
25 obtained by reacting the diphosphonic acid of formula:



and the amino-alcohol of formula:



are hereafter described.

Example 1

15 4-amino-1-hydroxybutane-1,1-biphosphonic acid,
 (alendronic acid, 1g, 4.016 mmoles), was dissolved into 20
 mL of CH_2Cl_2 / methyl alcohol (9:1). 2-amino-2-
 hydroxymethyl-1,3 propandiol, (trometamine, 486 mg, 4.016
 20 mmoles) dissolved in 5 mL of CH_2Cl_2 / methyl alcohol
 (9:1) was added under stirring to the alendronic acid
 solution. The white precipitate formed, was filtered and
 dried under vacuum.

1.263 g of alendronate trometamine salt were obtained,
 25 yield 85%.

Example 2

4-amino-1-hydroxybutane-1, 1-biphosphonic acid,
(alendronic acid, 1g, 4.016 mmoles), was suspended into
20 mL water. 2-amino-2-hydroxymethyl-1, 3 propandiol,
5 (trometamine, 486 mg, 4.016 mmoles) was added, under
stirring, to the aqueous solution of alendronic acid.
Solids rapidly dissolved in water, the suspension becomes
clear, while the resulting solution, having a pH = 4.18,
was frozen and lyophilised to give a white powder.

10 1.480 g of alendronate trometamine salt were obtained,
yield 99%.

Example 3

4-amino-1-hydroxybutane-1, 1-biphosphonic acid,
15 (alendronic acid, 1g, 4.016 mmoles), was suspended into 40
mL water. 2-amino-2-hydroxymethyl-1, 3 propandiol,
(trometamine, 972 mg, 8.032 mmoles) was added, under
stirring, to the aqueous solution of alendronic acid.
Solids rapidly dissolved in water, the suspension becomes
20 clear, while the resulting solution had a pH = 7.14 was
frozen and lyophilised to give a white powder.

1.97 g of alendronate trometamine salt were obtained,
yield 99%.

Example 4

4-amino-1-hydroxybutane-1, 1-biphosphonic acid, (alendronic acid, 1g, 4.016 mmoles), was suspended into 5 mL water. 2-amino-2-hydroxymethyl-1, 3 propandiol, trometamine (486 mg, 4.016 mmoles) was added, under stirring, to the aqueous solution of alendronic acid. Solids rapidly dissolved in water, the suspension became clear, while the resulting solution had a pH = 4.18. 10 mL of iso-propyl alcohol were added and the resulting solution was cooled at a temperature of -10 °C overnight. The precipitate formed was filtered, washed twice with cool iso-propyl alcohol, then was dried under vacuum.

743 mg of alendronate trometamine salt were obtained, yield 50%.

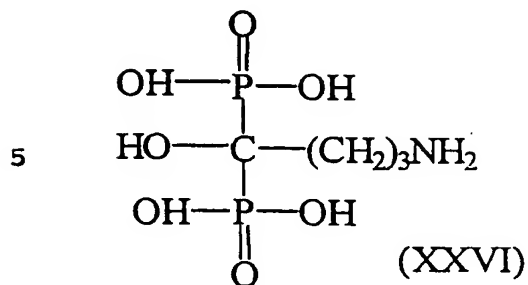
The product obtained according to the procedures reported in the examples 1, 2 and 4, was analysed by IR and ¹H-NMR spectroscopy.

The melting point was 180.53 °C.

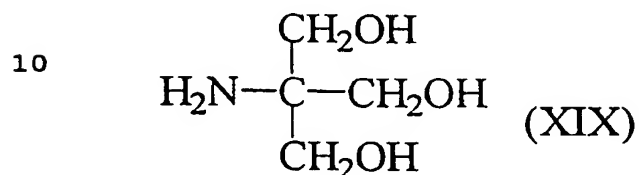
¹H-NMR (300 MHz), (D₂O) δ=3.615 (s 6H, CH₂O) ; 2.920 (t, 2H, N⁺-CH₂ , J=6.5 Hz); 1.900 (m, 2H, NCH₂ CH₂ CH₂); 1.890 (t, 2H, NCH₂ CH₂ CH₂ , J=6.5 Hz).

As an example, a non-limitative example is hereafter reported, referring to the preparation of a pharmaceutical formulation of the salt obtained by

reacting the diphosphonic acid of formula :



and the amino-alcohol of formula :



Example 5

15 Alendronate trometamine salt formulated in liposome matrix.

- LECINOL LS (liposomes) , 20%

- SALT OF 4-AMINO-1-HYDROXYBUTANE-1, 1-BIPHOSPHONIC ACID, (ALENDRONIC ACID) AND 2-AMINO-2-HYDROXYMETHYL-1, 3

20 PROPANDIOL, (TROMETAMINE) , 15%

(Ratio between alendronic acid and trometamine \cong 1:1)

- TROMETAMINE BASE; 1%

- CHOLESTEROL; 4%

- PROPYLENGLYCOL; 10%

25

- ETHANOL; 1%

- CARBOPOL ETD 2020; 0,5%

- Na₂EDTA ; 0.15%

- NIPAGIN; 0.2%

5 - PHENONIP (CONSERVATIVE); 0,3%

- CITRIC ACID; 0.2

- BHT; 0.01

- WATER; to 100 %

10 Dealing with the evaluation of the pharmaco-toxicological activity of the salts obtained by reacting diphosphonic acids of general formula (I) and amino-alcohols according to the present invention, biological tests were carried out taking as test compound the product alendronate trometamine obtained as described in the examples above.

15

EFFICACY

A study on a tissue culture (scalp slices of new-born mouse prepared according to the method described by A. Togari, Gen. Pharmacol. 24, 1133, 1993) was performed. At
20 the end of the culture period, the tissue added μ molar concentrations of the title product, was homogenised in saline plus 0.1% Triton X-100.

25

The obtained homogenate was used to determine alkaline phosphatase (as osteoblastic activity index) and N-acetylglycosaminidase (as osteoclastic activity index).

5 The test product starting from the 10 μ molar concentration, was shown to be able to activate in a significant manner the osteoblastic activity (alkaline phosphatase) and to inhibit the osteoclastic activity (N-acetylglycosaminidase).

10 TOXICITY

The compound when administered orally to mice at the dose of 50 mg/kg, which is a multiple (x300 times) of the human therapeutic dose, did not cause the onset of apparent toxic symptoms.

15

BIOAVAILABILITY

A study carried out in rats administered both orally and intravenously the test compound, alendronate trometamine, at the 10 mg/kg dose allowed calculation of a mean
20 absolute bioavailability equal to 8%. Calculation was performed on 0-24 hours urine elimination of alendronic acid according to the method described in J. of Chromatography, 533, 183-193, 1992: "Improved
25 determination of the biphosphonate alendronate in human

plasma and urine by automated pre-column derivatisation and HPLC with fluorescent and electro-chemical detection".

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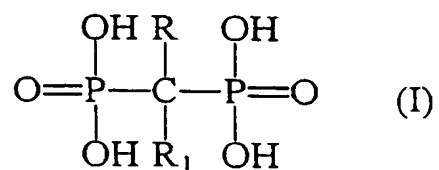
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CLAIMS

1. Diphosphonates or salts of diphosphonic acids and linear, branched, substituted and not substituted, cyclic, heterocyclic, aromatic amino-alcohol derivatives

5 having the following general formula:



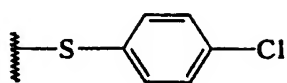
10 where $\text{R}=\text{R}_1$ or $\text{R}\neq\text{R}_1$ and R and R_1 are chosen among H, OH, Cl, linear or branched, substituted or not substituted alkyl groups, linear or branched, substituted or not substituted alkylidenic chain, or they are chosen among:

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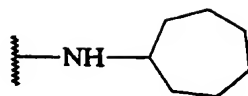
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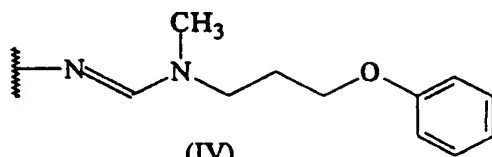


(II)



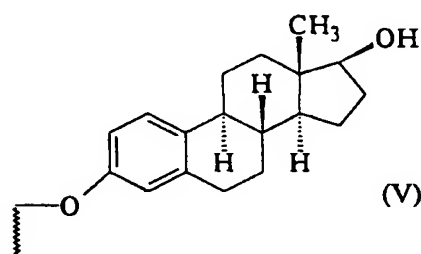
(III)

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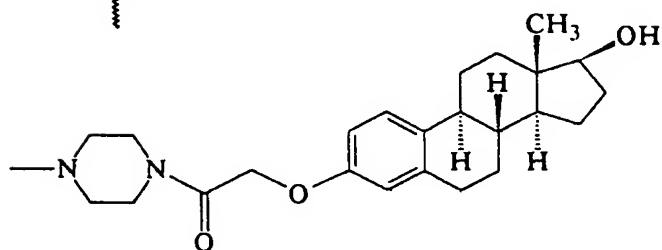
(IV)

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(V)

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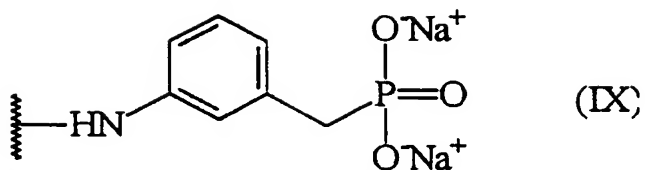
(VI)

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(VII)

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2. Diphosponates according to Claim 1, characterised by the fact that the mentioned amino-alcohols are chosen among linear and branched amino-alcohols, and specifically they are chosen among:

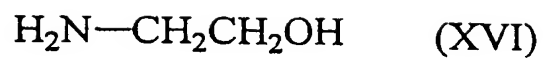
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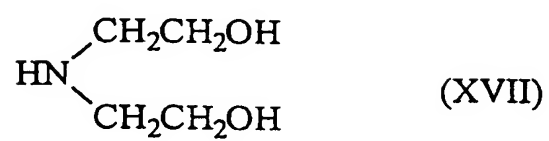
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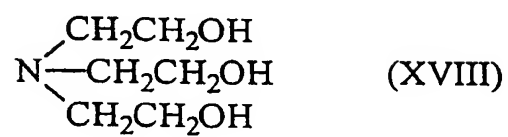
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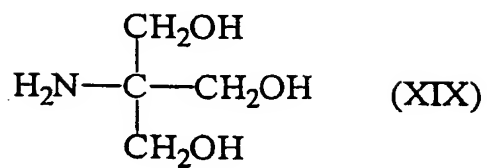
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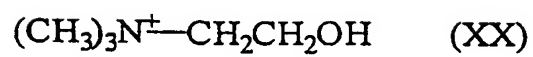
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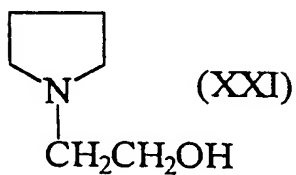


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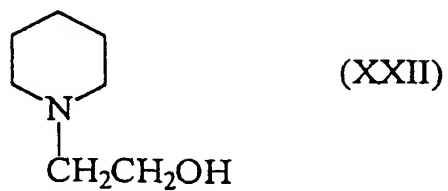


3. Diphosponates according to Claim 1, characterised by the fact that the mentioned amino-alcohols are cyclic and hetero cyclic amino-alcohols and are chosen among

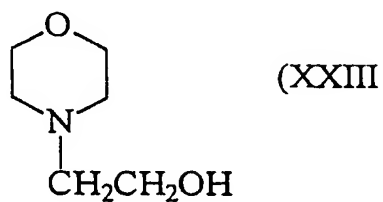
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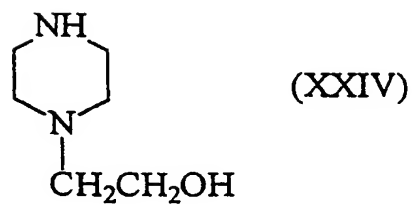
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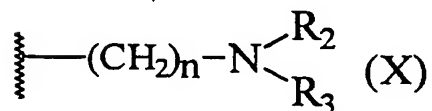
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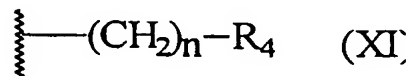
4. Diphosponates according to Claim 1, characterised by the fact that mentioned linear or branched substituted or non substituted alkylidenic chain , defined in formula (I), is chosen equal to:

5



with n within 1 and 6, where $\text{R}_2=\text{R}_3$ or $\text{R}_2\neq\text{R}_3$ and R_2 and R_3 are chosen among H, linear or branched, cyclic, substituted or not substituted alkyl groups, or R_2 and R_3 represent together with the nitrogen atom N an aliphatic or aromatic hetero-cycle.

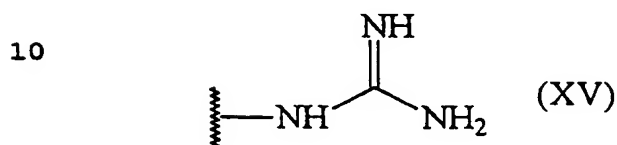
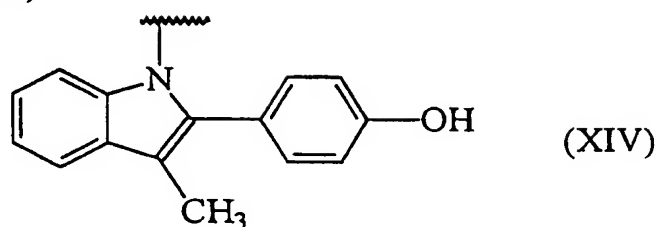
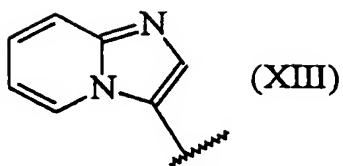
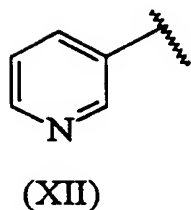
5. Diphosponates according to Claim 1. characterised by the fact that mentioned substituted alkylidenic chain, defined in formula (I), is also chosen equal to



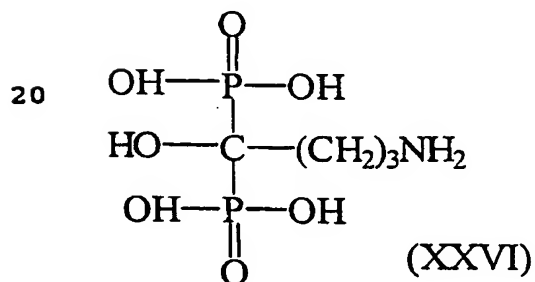
where n is within 1 and 6 and R_4 is chosen among:

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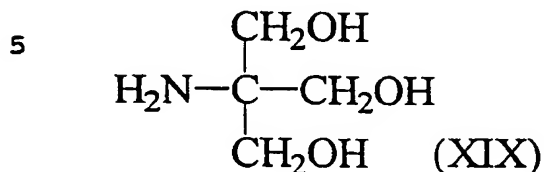
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6. Diphosponate according to Claim 1, characterised by the fact that is a salt obtained between a diphosphonic acid of general formula (I), where $R \neq R_1$, R is chosen equal to OH and R_1 is chosen as substituted linear alkyldienic chain of formula (X), where $n=3$, R_2 and R_3 are equal to H according to the following formula:



or 4-amino-1-hydroxybutane-1,1 bi-phosphonic acid (alendronic acid) and one branched amino-alcohol of formula



or 2-amino-2-hydroxymethyl-1,3-propanediol (trometamine).

7. Process for the preparation of diphosphonates according to claim 1, comprising the following steps:

- mixing of a diphosphonic acid of general formula (I) dissolved or suspended in appropriate solvent, with an amino-alcohol, possibly also dissolved in a proper solvent.
- 15 • Cooling of the mixture obtained and/or possible treatment with a proper solvent, to obtain a diphosphonate or salt of the mentioned diphosphonic acid of general formula (I) and the mentioned amino-alcohol
- 20 • Filtration, washing, possible purification and dryness (lyophilisation) of mentioned product (salt).

8. Use of diphosphonates or their salts between a diphosphonic acid of general formula (I) and amino-

alcohols as in Claim 1, for the treatment of osteoporosis,

5 9. Pharmaceutical compositions for the treatment of osteoporosis comprising at least one diphosphonate or a salt between a diphosphonic acid of general formula (I) and an amino- alcohol as in Claim 1, as active principle.

10 10. Pharmaceutical compositions, according to Claim 9, characterised by the fact that are prepared for parenteral (intravenous) administration.

11. Pharmaceutical compositions, according to Claim 9, characterised by the fact that includes liposomes or niosomes and proper carriers which allow the controlled release of the active principle.

12. Pharmaceutical compositions, according to Claim 9, characterised by the fact that they have the following composition:

20 - LECINOL LS (liposomes) , 20%
- SALT OF 4-AMINO-1-HYDROXYBUTANE-1, 1-BIPHOSPHONIC ACID, (ALENDRONIC ACID) AND 2-AMINO-2-HYDROXYMETHYL-1, 3 PROPANDIOL, (TROMETAMINE) , 15%

(Ratio between alendronic acid and trometamine \cong 1:1)

25 - TROMETAMINE BASE; 1%

- CHOLESTEROL; 4%
- PROPYLENGLYCOL; 10%
- ETHANOL; 1%
- CARBOPOL ETD 2020; 0,5%
- 5 - Na₂EDTA ; 0.15%
- NIPAGIN; 0.2%
- PHENONIP (CONSERVATIVE); 0,3%
- CITRIC ACID; 0.2
- BHT; 0.01
- 10 - WATER; to 100 %

13. Pharmaceutical composition, according to Claim 12,
characterised by the fact that is under liposomal form

14. Diphosphoates according to Claim 1, characterised by
the fact that molar ratios between mentioned
15 diphosphonic acids and the amino-alcohols are in a
molar ratio between 1:1 and 1:2.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/04238

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07F9/38	A61K31/66	C07F9/576	C07C215/04	C07D295/08
	C07J51/00	A61K9/127	C07F9/572	C07F9/58	C07F9/6561

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07F C07C C07D C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	GB 2 118 042 A (INSTITUTO GENTILI SPA) 26 October 1983 cited in the application see the whole document	1-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- "&" document member of the same patent family

Date of the actual completion of the international search

20 October 1998

Date of mailing of the international search report

05/11/1998

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Beslier, L

INTERNATIONAL SEARCH REPORT

Int l Application No
PCT/EP 98/04238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	FR 2 142 051 A (HERCULES INC.) 26 January 1973 see example 23; table III ---	1,2
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X	US 4 830 779 A (SEIJI MAENO) 16 May 1989 see column 3, line 57-60 ---	1,2
X	GB 1 508 772 A (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ BV) 26 April 1978 see examples 36,39,45 ---	1,2
X	US 5 389 261 A (JOHN DALY) 14 February 1995 see claims 2,6,7; example 8 ---	1,2
X	EP 0 781 804 A (KAO CORP.) 2 July 1997 see page 7; example 27 ---	1,2
X	DD 273 650 A (VEB ROBOTRON-ELEKTRONIK RADEBERG) 22 November 1989 see example 4 ---	1,2
X	DD 150 744 A (WOBST, SIGURD) 16 September 1981 see page 8; example 2 -----	1,2

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Information on patent family members

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